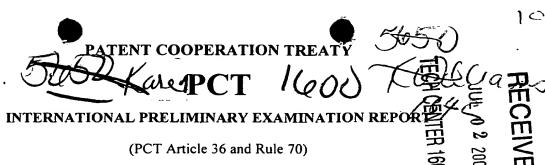
7ranslation



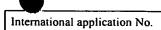
Applicant's or agent's file reference K 2675

International application No. International filing date (day/month/year) PCT/DE99/01350

International Patent Classification (IPC) or national classification and IPC C07K 16/00

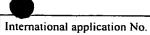
Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG DES ÖFFENTLICHEN RECHTS

Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG DES ÖFFENTLICHEN RECHTS					
This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.					
2. This REPORT consists of a total of 8 sheets, including	g this cover sheet.				
been amended and are the basis for this report and/or sheets	This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).				
These annexes consist of a total of sheets.					
3. This report contains indications relating to the following items:					
Basis of the report					
II Priority					
III Non-establishment of opinion with regard to novel	ty, inventive step and industrial applicability				
IV Lack of unity of invention	IV Lack of unity of invention				
Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement					
VI Certain documents cited					
VII Certain defects in the international application					
VIII Certain observations on the international application					
٠					
Date of submission of the demand Date of	completion of this report				
03 December 1999 (03.12.99)	21 August 2000 (21.08.2000)				
Name and mailing address of the IPEA/EP  Author	zed officer				
Facsimile No. Telepho	one No.				



## PCT/DE99/01350

I. Basis of the	•				世
1. This report	t has been drawn of	on the basis of	(Replacement sheet	is which have been furnished to the and are not annexed to the re	he receiving Office in response to an invitation port since they do not contamamendments.):
				,	ori since they do not consumate of 2 2002
	the international	l application as	s originally filed.		2 2 ER
$\boxtimes$	the description,	pages	1-15	_, as originally filed,	2002
		pages		_, filed with the demand,	) <sub>129</sub>
		pages		_, filed with the letter of _	
		pages		_, filed with the letter of _	
$\boxtimes$	the claims,	Nos.		_, as originally filed,	
		Nos.		, as amended under Article	19,
		Nos		_ , filed with the demand,	
		Nos	1-21	_ , filed with the letter of _	31 July 2000 (31.07.2000)
					·
$\boxtimes$	the drawings,	sheets/fig	1/10-10/10	_ , as originally filed,	
لكا	-			_ , filed with the demand,	
2. The amend	lments have resulte	ed in the cance	ellation of:		
	the description,				
	the claims,				
	•				
لــا	the drawings,	sneets/fig			
3. This	report has been e	stablished as if	f (some of) the am	nendments had not been made	e, since they have been considered
to go	beyond the disclo	osure as filed,	as indicated in the	e Supplemental Box (Rule 70.	.2(c)).
4. Additional	observations, if no	ecessary:			•
See	Suppleme	ntal BO	K		



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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability				
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be industrially applicable have not been examined in respect of:	non obvious), or to be			
the entire international application.				
Claims Nos				
because:				
the said international application, or the said claims Nos. 20 and 21 relate to the following subject matter which does not require an international preliminary exception.	amination (specify):			
See Supplemental Box				
the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):				
are so unclear that no meaningful opinion could be formed (specify):				
the claims, or said claims Nos. by the description that no meaningful opinion could be formed.	are so inadequately supported			
no international search report has been established for said claims Nos.				

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#### I. Basis of the report

- 1. This report has been drawn on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):
  - a) It was not possible for the International Preliminary Examination Authority to examine whether the protocol sequence submitted with the letter of 5 January 1999 goes beyond the content of the application as originally filed.
  - b) Therefore, the examination is based on the version of the protocol sequence as originally filed.

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SII	nn	lem	en	tai	Box
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(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 20 and 21 refer to a subject matter which, in the opinion of this authority, falls under PCT Rule 67.1(iv). Therefore, a report is not carried out as to the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

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V.	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
	citations and explanations supporting such statement

1.	Statement			
	Novelty (N)	Claims	1-21	YES
		Claims		NO
	Inventive step (IS)	Claims	1-21	YES
		Claims		NO NO
	Industrial applicability (IA)	Claims	1-19	YES
		Claims		NO NO

2. Citations and explanations

Reference is made to the following documents cited in the international search report:

D1: Journal of Immunology, 152(11), 1994, 5368-74

D2: Proceedings of the National Academy of Sciences of the

United States of America, 92(15), 1995, 7021-5

D3: Journal of Immunology, 154(9), 1995, 4576-82

D4: Molecular Immunology, 32(17-18), 1995, 1405-12

D5: Journal of Molecular Biology, 293(1), 1999, 41-56.

Document D5 was published after the filing date of the application. It describes the bivalent and tetravalent  $F_v$  antibody constructs of the invention. Both inventors are named in D5. Therefore, this T-document can be a useful aide to understanding the invention.

- a) Novelty (PCT Article 33(2))
- (i) Documents D1 to D4\* describe (a) bispecific  $F_{\nu}$  antibody constructs with four variable domains which are combined with peptide linkers, (b) coding expression plasmids for such constructs, and (c) methods for producing such constructs, wherein coding DNAs for the peptide linkers are linked to

the coding DNAs for the four variable domains of an  $F_{\nu}$  antibody construct in such a way that the peptide linkers join the variable domains and the DNA molecule obtained therefrom is expressed in an expression plasmid.

\*D1: see pages 5369-5370

\*D2: see pages 7021-7022

\*D3: see pages 4577-4578

\*D4: see pages 1406-1408.

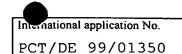
The peptide linkers have:

- 14 and 25 amino acids in D1 (see Figure 1, page 5370),
- 5 and 15 amino acids  $[Gly_4-Ser_1 \text{ and } (Gly_4-Ser_1)_3]$  in D2 (see Figure 1, page 7022),
- 14 and 15 amino acids in D3 [ $(Gly_4-Ser_1)_3$ ] (see Figure 1, page 4578), and
- 15 amino acids in D4 [(Gly<sub>4</sub>-Ser<sub>1</sub>)<sub>3</sub>] (see Figure 1, page 1407).
- (ii) None of documents D1 to D4 describes a multivalent  $F_{\nu}$  antibody construct joined by the peptide linkers 1, 2 and 3, in which the peptide linkers 1 and 3 have 0-10 amino acids. Consequently, the subject matter of Claim 1 can be deemed novel over the cited prior art. The same applies to the subjects of Claims 2-21 because they refer back to Claim 1.
- b) <u>Inventive step</u> (PCT Article 33(3))
- (i) The bispecific  $\text{scF}_{\nu}$  antibody molecules of D1-D4 are able to fold themselves so that a  $V_L$  domain is joined to an adjacent corresponding  $V_L$  domain. This

disadvantage is avoided in the invention due to the short peptide linkers 1 and 3 of the  $\mathrm{scF}_v$  antibody construct. Thus, an  $\mathrm{scF}_v$  antibody construct as per the invention can be joined to other  $\mathrm{scF}_v$  antibody constructs, producing  $\mathrm{F}_v$  antibody constructs with four or eight variable domains and a plurality of valences and specificities. Thus, the subject matter of Claim 1 involves an inventive step with respect to the cited prior art. The same applies to the subjects of Claims 2-13, 20 and 21 because they refer back to Claim 1.

- (ii) The expression plasmids of Claims 14-19 code for bivalent  $F_{\nu}$  antibody constructs with four variable domains having two peptide linkers "GG" and one peptide linker having either 12 (("GGPGS" + 7 additional amino acids) or 27  $(G_4S_1)_4$  + 7 additional amino acids) (see document D5, page 42, right-hand column). Since two such constructs (with such a combination of peptide linkers) can fold themselves together so as to form stable tetravalent  $F_{\nu}$  antibody constructs with eight variable domains, the bivalent constructs as characterised in Claim 1 could be deemed inventive. Consequently, the subject matter of Claims 14-19 can also be deemed inventive.
- c) Industrial applicability (PCT Article 33(34))
- (i) The subject matter of the present Claims 1-19 appears to be industrially applicable.
- (ii) The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of Claims 20 and 21 in their present form. Patentability can also depend on the wording of the





claims. The EPO, for example, does not recognise the industrial applicability of claims to the use of a compound in a medical treatment; it does, however, allow claims to the first use of a known compound in a medical treatment or to the use of such a compound in the manufacture of a drug for a new medical application.



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#### VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

- a) In contrast to lines 20 and 21 of page 9 of the description, Figure 6 does not indicate the complete nucleotide and protein sequences of the tetravalent  $F_{\nu}$  antibody constructs.
- b) In contrast to the final sentence of Example 2 on page 10 of the description, Figure 7 does not show the nucleotide and protein sequences of the tetravalent  $F_v$  antibody construct (see the final sentence of Example 2 on page 10). A nucleotide and protein sequence is only outlined for the  $F_v$  antibody construct with four variable domains (cf. Fig. 1). There is no description of a gene that codes for a tetravalent  $F_v$  antibody construct.

#### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

a)  $F_v$  antibody constructs with eight variable domains, that is, <u>tetravalent</u> constructs, which are also described in the application, are dimers consisting of two  $F_v$  antibody constructs with four variable domains. An  $F_v$  antibody construct such as this with eight variable domains arises if two <u>independent</u> (meaning that these constructs are not joined to any peptide linker) single-chain  $F_v$  antibody constructs with four variable domains are folded together (see also D5, pages 43 and 44).

The application does not describe any  $F_{\nu}$  antibody constructs with twelve or sixteen or more variable domains. In addition, the description does not explain how such an  $F_{\nu}$  antibody construct could be produced.

By using the word "multivalent", the claimed subject matter encompasses constructs containing more than four or eight variable domains. Consequently, Claims 1-13, 20 and 21 violate PCT Article 6.

Although the claims mention three peptide linkers 1, 2 and 3, Figures 3, 4, 5, 6, 9 and 10 mention F<sub>v</sub> antibody constructs with four variable domains containing two peptide linkers and one mean peptide linker 2 or 3. Due to this inconsistency between the description and the claims, Claims 1-14 and Claims 21 and 22 also violate PCT Article 6. In this context, it appears that the peptide linkers should not be characterised with numbers alone.

b)